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Hepatitis C Infection Is Associated with Lower Lipids and High-Sensitivity C-Reactive Protein in HIV-Infected Men

MICHELLE FLORIS-MOORE, M.D., M.S.[1,2], **ANDREA A. HOWARD, M.D., M.S.**[1,2], **YUNGTAI LO, Ph.D.**[1], **ELLIE E. SCHOENBAUM, M.D.**[1,2,3], **JULIA H. ARNSTEN, M.D., M.P.H.**[1,2,4], and **ROBERT S. KLEIN, M.D.**[1,2]

1*Department of Epidemiology & Population Health, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York.*

2*Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York.*

3*Department of Obstetrics, Gynecology & Women's Health, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York.*

4*Department of Psychiatry, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York.*

Abstract

Increased cardiovascular risk has been linked to HIV infection and combination antiretroviral therapy, but the impact of hepatitis C virus (HCV) status on indices of cardiovascular risk has not been routinely assessed in the HIV-infected population. The objective of this study was to analyze associations of HCV, HIV, and combination antiretroviral therapy with lipid levels and C-reactive protein (CRP) among older men. We measured fasting total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and high-sensitivity CRP serum levels in a cross-sectional study of 108 HIV-infected and 74 HIV-uninfected at-risk older men. One hundred ten men (60%) had detectable HCV RNA, with no difference by HIV status ($p = 0.25$). The majority (88%) of men with HCV infection had a history of injection drug use. Among all men, HCV infection was independently associated with lower total cholesterol ($p < 0.001$), LDL-C ($p < 0.001$), triglycerides ($p = 0.01$), and CRP ($p < 0.001$). Among HIV-infected men, HCV infection was associated with lower total cholesterol ($p < 0.001$), LDL-C ($p < 0.001$), and CRP ($p = 0.004$). HCV infection was associated with lower triglycerides among men on protease inhibitors (PI) ($p = 0.02$) and non-PI combination antiretroviral therapy ($p = 0.02$), but not among antiretroviral-naïve men. These findings demonstrate an association of lower serum lipid and CRP levels with HCV infection and suggest that HCV status should be assessed as an important correlate of cardiovascular risk factors in studies of older men with or at risk for HIV.

INTRODUCTION

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART), which has greatly improved survival among HIV-infected persons, has been linked to dyslipidemia and increased cardiovascular risk.[1–5] HIV infection is also associated with C-reactive protein (CRP), a more recently identified cardiovascular risk factor.[6] However, studies of cardiovascular disease among HIV-infected persons have not consistently shown increased rates of atherosclerosis in association with HIV

Address reprint requests to: Michelle Floris-Moore, M.D., M.S. AIDS Research Program Montefiore Medical Center 111 East 210th Street Bronx, NY 10467 E-mail: mfloris@montefiore.org.

infection or HAART use.[3–5,7–9] Investigation of other factors that may influence cardiovascular risk in the HIV-infected population is therefore important.

Reported hepatitis C virus (HCV) coinfection rates range from 4% among HIV-infected non-drug users to 89% among HIV-infected injection drug users (IDUs).[10–14] In a recent study of men who have sex with men, 26% of men who reported that they were HIV-infected were also HCV-infected.[15] Hypocholesteremia has been associated with HCV infection in both the general population and among HIV-infected persons.[16–18] Among persons with liver disease, hypocholesteremia may in some cases indicate decreased hepatic function and poor prognosis, however, lower total cholesterol and low-density lipoprotein cholesterol (LDL-C) have been reported with HCV infection independent of hepatic fibrosis or synthetic function.[16–18] Hepatitis C infection has also been linked to lower CRP levels.[19,20] Because CRP is produced mainly by hepatocytes, it has been postulated that lower CRP in HCV-infected patients may reflect hepatocellular injury.[20]

It is therefore possible that HCV coinfection may, to some extent, ameliorate the increased cardiovascular risk indices that have been reported in HIV-infected persons. Our study sought to investigate associations of HCV with lipid and CRP levels in a well-characterized cohort of older HIV-infected and at-risk men, with high prevalence of HCV-infection, in the Bronx, New York.

MATERIALS AND METHODS

Study design and participants

We performed a cross-sectional analysis of lipid and CRP levels among men participating in the Cohort of HIV At-Risk Aging Men's Prospective Study (CHAMPS), an ongoing longitudinal study of atherosclerosis, bone loss, and drug use in older men with or at risk for HIV infection recruited from the community in the Bronx, New York. Study design and participant recruitment have been described in detail previously.[21] In brief, men within 1 year of their fiftieth birthday or older were eligible if they had HIV infection or were at risk for acquiring HIV through injection drug use, unprotected sex with men, having had five or more sexual partners within the prior 5 years, having exchanged sex for drugs or money, or having had unprotected sex with an injection drug user or with a woman known to have HIV infection. Participants attend semiannual research visits for standardized interviews, phlebotomy, and measurement of weight, height, waist circumference, and blood pressure. Between March 2003 and July 2004, 217 men in CHAMPS had fasting lipid and CRP levels measured. The Instituutional Review Boards at Montefiore Medical Center and Albert Einstein College of Medicine approved this study. All participants gave written informed consent.

Study procedures

Standardized interviews collected data on sociodemographic characteristics, HIV/HCV transmission risk factors, medical history, HIV disease status, antiretroviral and other medication use, alcohol use, cigarette smoking, diet, physical activity, and drug-use behaviors. Detailed information was collected on type (cocaine, heroin, or speedball) and route (injection, smoking, or snorting) of drug use. HIV/HCV transmission risk factors among the men in our study were classified as injection drug use, high-risk sexual activity (sex with an injection drug user or an HIV-infected partner, sex with men, exchanging sex for drugs/money, or having multiple sexual partners, defined as 5 or more partners within the past 5 years), or blood/blood product transfusion risk. Risk categories were not mutually exclusive, because it was possible for an individual to have more than one risk factor.

Dietary intake was measured using the modified Rapid Eating and Activity Assessment for Participants interview.[22] Body mass index (BMI) was calculated as weight/(height)^2 (kg/m^2).[23] Hypertension was defined as systolic blood pressure 130 mm Hg or more and/or diastolic blood pressure 85 mm Hg or more (mean of two measurements taken while the participant was sitting). Men who reported a history of hypertension and current use of antihypertensive medications were classified as hypertensive regardless of measured blood pressure.

For HIV-infected men, CD4 lymphocyte count and HIV viral load were measured at each visit, and for seronegative men, HIV serology repeated. Participants underwent oral glucose tolerance testing with phlebotomy for glucose determination immediately prior to, and 120 minutes after, ingestion of a 75-g glucose beverage.[24] Fasting insulin was measured by double antibody radioimmunoassay in the Hormone Assay Core of the Einstein Diabetes Research and Training Center (intra-assay coefficient of variance, 7.2%; interassay coefficient of variance, 9.4%; cross-reactivity with proinsulin, 36.8%), and plasma glucose measured by hexokinase method. Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR).[25] Impaired glucose tolerance and diabetes were defined using American Diabetes Association criteria.[26]

Determination of hepatitis C status

Hepatitis C virus testing was performed using enzyme immunoassay (ELISA 3.0, Ortho Diagnostic Systems, Rochester, NY). For HCV seropositive participants, HCV ribonucleic acid (RNA) was quantified using the VERSANT HCV RNA assay (Bayer Corporation, Tarrytown, NY), with a lower limit of detection of 615 IU/mL. Hepatitis C infection was defined by the presence of HCV RNA.

Antiretroviral therapy classification

Published guidelines in use at study initiation were used to define HAART.[27] Protease inhibitor-based HAART was defined as three or more ARV medications including at least one PI, and non-PI HAART as three or more ARV medications including at least one non-nucleoside reverse transcriptase inhibitor (NNRTI) or abacavir. Men were classified as being either (1) HIV-uninfected; (2) HIV-infected and antiretroviral-naïve (ARV-naïve); (3) HIV-infected and naïve to protease inhibitors (PIs) but currently taking non-PI HAART; or (4) HIV-infected and currently taking PI-based HAART.

Outcome measurement

Blood was drawn after a 10- to 12-hour overnight fast. Serum was separated within 20 minutes of collection and stored at −70°C until the day of the assay. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were assayed by routine laboratory techniques using Lipids Research Clinics methodology.[28] The low density lipoprotein cholesterol (LDL-C) level was measured directly (Olympus Diagnostics, Olympus America Inc., Melville, NY) because for patients with triglycerides greater than 400 mg/L, the Friedewald formula may be inaccurate.[29] C-reactive protein was measured by high-sensitivity enzyme-linked immunosorbent assay (ELISA; ALPCO, Windham, NH) with intra-assay and interassay coefficients of variance of 7.04% and 11.04%, respectively, and a lower limit of detection of 0.002 mg/L.

Data analysis

Univariate analyses were performed using χ^2, Fisher's exact, Student's *t*, Wilcoxon, or Kruskal-Wallis tests, as appropriate. Linear regression models were used to assess associations of HCV infection with total cholesterol, LDL-C, HDL-C, triglycerides, and CRP. Variables examined

included HIV status, age, BMI, waist circumference, HOMA-IR, dietary intake, drug use and cigarette smoking, number of years since first injection drug use; and among HIV-infected men, HIV-1 viral load, CD4 cell count, and antiretroviral therapy group; as well as those factors with $p \leq 0.2$ on univariate analyses.

Age was classified as less than or the median or greater value of 54 years. BMI and waist circumference were each explored as continuous variables in separate models. Dietary intake was classified as high in fiber and low in fat if participants reported rarely eating less than three servings of whole-grain/high-fiber products daily and had a dietary fat score at or below the median of the study population. Cocaine and heroin use were explored both as a combined variable and individually. Number of years since first injection drug use was included in the models as a surrogate for duration of HCV infection, because other studies have shown that acquisition of HCV infection occurs rapidly upon initiation of injection drug use, with 78% of drug users being HCV antibody-positive within the first year of injecting.[30]

Multivariate analyses were performed for the entire study sample and then separately for HIV-infected men. In the models for HIV-infected men, HIV-1 viral load was categorized as detectable (≥75 copies per milliliter) or undetectable. CD4 cell count was categorized as less than 200 cells/mm^3, 200−499 cells/mm^3, and 500 cells/mm^3 or more. With respect to antiretroviral use, participants were classified as being (1) antiretroviral-naïve (ARV-naïve), (2) naïve to PIs but on non-PI HAART, or (3) on PI-based HAART. Triglycerides, HDL-C, and CRP were log-transformed in order to meet normality criteria for linear regression. Interaction terms were tested and model fit examined. Statistical analyses were performed using SPSS® (base 10.0, SPSS Inc., Chicago, IL) and SAS® (version 8.1, SAS Institute, Cary, NC) software. Statistical significance was determined using two-tailed tests with $p < 0.05$ considered to be significant.

RESULTS

Participant characteristics

Of the 217 men enrolled who had lipid levels, 24 had a history of a myocardial infarction or stroke and were therefore excluded from this analysis. No men were taking lipid-lowering medications. Hepatitis C results were available for 182 of the 193 men who were not excluded. One hundred ten men (60.4%) had detectable HCV RNA, and were classified as HCV-infected. Of the remaining 72 men, 48 men were anti-HCV negative and 24 were anti-HCV positive but had no detectable HCV RNA. Seventeen men (9%) reported ever receiving treatment for HCV infection and the two men (0.6%) reported use of interferon within 6 months prior to the study interview.

Men excluded from the study because of reported prior stroke or myocardial infarction did not differ significantly from those included with respect to the prevalence of HCV infection (66.7% *vs*. 60.4%, ($p = 0.56$), levels of total cholesterol ($p = 0.56$), LDL-C ($p = 0.72$), or triglycerides ($p = 0.28$), or CRP levels ($p = 0.51$). There were also no significant differences in lipid or CRP levels when excluded and included men were analyzed separately within the HCV-infected and HCV-uninfected groups.

Participant characteristics are shown in Table 1.

The median age was 54 years among both HCV-infected and HCV-uninfected men. Most men (89.1% of HCV-infected men and 87.5% of uninfected men) were aged 50−60 years, while 9.1% of HCV-infected and 9.7% of uninfected men were aged 61−70 ($p = 0.97$). Three men (2 HCV-infected and 1 uninfected) were over age 70. Ninety-seven of 118 HCV-infected men (88%) had ever injected drugs compared to 29% of HCV-uninfected men ($p < 0.001$). Similarly,

a greater proportion of HCV-infected than HCV-uninfected men were currently using illicit drugs. The median number of years since first injection drug use was 35 years among HCV-infected men and 34 years among uninfected men ($p = 0.21$). Most men (92.3%) were either past or current cigarette smokers. HCV-infected men were more likely than HCV-uninfected men to smoke currently ($p = 0.002$), although pack-years of smoking did not differ between the HCV groups. Waist circumference, BMI, and dietary fiber/fat intake did not differ by HCV status.

One hundred eight men (59.3%) were HIV-infected, 69 (63.9%) of whom were coinfected with HCV. There was no significant difference in HCV prevalence by HIV serostatus. The median CD4 lymphocyte count among HIV-infected men was 342 cells/mmn (interquartile range [IQR] 216−522) and 57.4% had detectable HIV-1 viral load (>75 copies per milliliter). Approximately half of the HIV-infected men (54.6%) were taking PI-HAART, 21.3% were on non-PI HAART, and 24.1% were ARV-naïve.

Univariate analysis of lipid levels

Table 2 shows univariate analysis of lipid results. In the overall study sample, HCV-infected men had significantly lower mean total cholesterol ($p < 0.01$) and LDL-C ($p < 0.01$) than HCV-uninfected men. Triglycerides ($p = 0.07$) and HDL-C ($p = 0.81$) did not differ by HCV status. Among HIV-infected men, HCV infection remained significantly associated with lower total cholesterol and LDL-C.

HIV-infected men had lower mean total cholesterol (152.0 4.1 versus 165.6 4.8 mg/dL, $p < 0.01$) and HDL-C (42.6 ± 1.6 versus 48.7 ± 1.6 mg/dL, $p < 0.01$), but higher triglycerides (134.9 ± 9.2 versus 106.0 ± 8.6 mg/dL, $p < 0.01$) than HIV-uninfected men. Among the HIV-infected men, PI use was associated with the highest total cholesterol (159.6 ± 5.8 mg/dL versus 132.8 ± 7.1 [ARV-naïve] and 154.3 ± 8.4 [non-PI HAART], $p = 0.01$) and triglycerides (150.1 ± 12.7 mg/dL versus 121.2 ± 22.8 and 111.3 ± 10.6, respectively, $p = 0.045$).

Multivariate analysis of lipids levels

Results of separate multivariate analyses in the overall study sample (Table 3) and among HIV-infected men (Table 4) showed that being HCV-infected was associated with lower total cholesterol, LDL-C, and triglycerides. HCV status was not associated with HDL-C ($p = 0.92$ in the overall sample, $p = 0.99$ among HIV-infected men, data not shown).

After adjusting for HIV status, HOMA-IR, dietary intake of fat and fiber, and age, HCV-infected men had total cholesterol 32.51 mg/dL lower (95% confidence interval [CI] −44.52, −20.50; $p < 0.001$), and LDL-C 22.23 mg/dL lower (95% CI −31.20, −13.21; $p < 0.001$) than HCV-uninfected men. The effect on triglycerides was of smaller magnitude, with HCV-infected men having triglyceride levels 1.23 mg/dL lower than HCV-uninfected men, after adjusting for the covariates listed above ($p = 0.01$; data back-transformed). HIV-infected men had higher triglycerides ($p = 0.001$) than HIV-uninfected men. HOMA-IR was positively associated with triglycerides ($p = 0.01$) and LDL-C ($p = 0.03$).

Among HIV-infected men (Table 4), after adjusting for antiretroviral group, HIV-1 viral load, HOMA-IR, dietary fiber and fat intake, and age, HCV-infected men had lower total cholesterol ($p < 0.001$) and LDL-C ($p < 0.001$). The effect of HCV infection on triglycerides was modified by the antiretroviral group. Being HCV-infected was associated with lower triglycerides among men on PI HAART and non-PI HAART, but not among ARV-naïve men. Among PI-users, those who were HCV-infected had triglycerides 1.41 mg/dL lower than HCV-uninfected men ($p = 0.02$), while among men on non-PI HAART, those who were HCV-infected had triglycerides 1.58 mg/dL lower than HCV-uninfected men ($p = 0.02$). Among HCV-uninfected

men, use of PI-HAART was associated with triglycerides 2.18 mg/dL higher compared to being ART-naïve ($p = 0.001$).

Among HIV-infected men, a detectable HIV-1 viral load was associated with lower total cholesterol ($p = 0.04$). A similar association with LDL-C did not reach statistical significance ($p = 0.06$). CD4 cell count was not significantly associated with total cholesterol ($p = 0.68$), LDL-C ($p = 0.95$), or triglycerides ($p = 0.55$), and its inclusion in the multivariate models did not change associations of HCV infection with these outcomes. Low-fat, high-fiber dietary intake was significantly associated with lower total cholesterol ($p = 0.049$) but not with LDL-C or triglycerides. Insulin resistance (HOMA-IR) remained positively associated with triglycerides ($p = 0.049$). Current cigarette smoking, pack-years of cigarette smoking, Current cigarette smoking, pack-years of cigarette smoking, heroin use, cocaine use, and number of years since first injection drug use were not associated with lipid levels in the overall study sample or among HIV-infected men.

Because a single undetectable HCV RNA level cannot exclude active infection, we repeated multivariate models for each outcome variable, comparing men with detectable HCV RNA levels to those known to be HCV-uninfected (i.e., negative for HCV antibody), after excluding men who were anti-HCV positive but had no detectable RNA. The statistical significance and magnitude of the association of HCV status with lower total cholesterol and LDL-C were essentially unchanged in these models. The association with triglycerides, while unchanged in the analysis of HIV-infected men, did not reach significance in the overall study sample ($p = 0.11$).

Univariate analysis of CRP

CRP results were available for 158 of 182 (87%) men (Table 2). Median CRP was 1.43 mg/L (IQR 0.57, 3.58). Sixty-one men (38.6%) had CRP less than 1 mg/L, 54 (34.2%) had CRP between 1 and 3 mg/L, and 43 (27.2%) had CRP greater than 3 mg/L. Waist circumference ($r = 0.27$, $p < 0.01$) and BMI ($r = 0.23$, $p < 0.01$) were positively correlated with CRP. Overall, HCV-infected men had significantly lower median CRP than HCV-uninfected men (1.03 versus 1.86 mg/L, $p = 0.04$). There was no significant difference in CRP between HCV-infected men who had ever received hepatitis C treatment and those who had not (1.84 mg/dL versus 1.01 mg/dL, $p = 0.69$). Among HIV-infected men, however, the difference based on HCV status was not statistically significant (1.30 mg/L among HCV-infected men versus 1.78 mg/L among HCV-uninfected, $p = 0.62$). HIV serostatus was not significantly associated with CRP ($p = 0.33$). Among HIV-infected men antiretroviral group, CD4 lymphocyte count, and HIV-1 viral load were not associated with CRP.

Multivariate analysis of CRP

HCV-infected men had significantly lower CRP in multivariate analysis of both the overall study sample (Table 3) and among HIV-infected men (Table 4). After adjusting for HIV status, waist circumference, pack–years of cigarette smoking, and age, HCV-infected men had CRP 2.47 mg/L lower than HCV-uninfected men ($p < 0.001$). Waist circumference ($p = 0.001$) and pack–years of smoking ($p = 0.003$) were positively associated with CRP. HIV status was not associated with CRP.

Exclusion of those men who reported ever receiving HCV treatment from the sample did not change the significance or magnitude of associations for the covariates in the model.

Among HIV-infected men, after additionally adjusting for antiretroviral group and viral load, HCV-infected men had CRP 2.44 mg/L lower than HCV-uninfected men ($p = 0.004$). There was no significant association of CD4 cell count with CRP ($p = 0.60$) and its inclusion in the

multivariate model did not change the association of HCV infection with lower CRP levels. Heroin use, cocaine use, and number of years since first injection drug use were not associated with CRP in either model. A separate model of CRP comparing HCV-infected men to anti-HCV negative men did not change the magnitude or significance of these associations.

DISCUSSION

This study of a well-characterized cohort of HIV-infected and at-risk men, in or older than the fifth decade of age, found a strong association between HCV-infection, defined by the detection of HCV RNA, and lower total cholesterol, LDL-C, triglyceride, and CRP levels. This association was highly significant in both the overall study sample as well as in men who were HIV-infected. Among HIV-infected men, HCV modified the effect of PIs on triglycerides so that HCV coinfected PI users had lower triglycerides than HCV-uninfected PI users. Our findings confirm previous reports associating HCV infection with lower lipid levels and provide new evidence of its association with lower CRP levels in the HIV-infected population.[16,31,32]

Among HIV-infected men, HCV coinfection was associated with differences in total cholesterol (33.7 mg/dL lower than HCV-uninfected men) and LDL-C (23.2 mg/dL lower) that would be considered clinically meaningful. Similar differences in total cholesterol and LDL-C based on HCV antibody status have been reported by Polgreen et al.[16] While they reported no HCV effect on triglycerides, we found a small but statistically significant decrease in triglycerides associated with HCV infection among men on HAART, but not among ART-naïve men. Likewise, Collazos et al.[33] reported markedly lower rates of hyperlipidemia, (total cholesterol or triglycerides greater than 200 mg/dL) in association with HCV among HAART users but not among non-HAART users. In that longitudinal study, and in a similar cohort study by Patroni et al.,[32] HCV coinfection predicted smaller HAART-associated increases in lipids compared to being HCV-uninfected.[33]

The biologic mechanism underlying the lower lipid levels seen in association with HCV infection has not been determined. Because the liver plays a pivotal role in cholesterol synthesis, impairment of hepatic synthetic function induced by chronic active hepatitis may lead to decreased secretion of very low-density lipoprotein (VLDL) and thus to lower total cholesterol and LDL-C levels. Although some studies have shown associations between reductions in lipid levels and histopathologic liver damage or hepatic inflammation,[34,35] others have reported no significant associations.[17,36]

Lower lipid levels have been reported in patients with chronic hepatitis caused by HCV infection compared to those with Hepatitis B infection, suggesting an HCV-specific effect on lipids, either as a result of differential effects on liver function or a direct interaction with lipid metabolism.[36] Some studies suggest that HCV core protein decreases activity of microsomal triglyceride transfer protein, leading to decreased hepatic VLDL assembly and secretion.[37,38] In addition, there is evidence that HCV particles associate with LDL and VLDL particles in plasma and utilize the LDL receptor for cell binding, possibly leading to increased lipid uptake by cells.[39,40] Lower serum lipid levels have been reported in HCV-infected patients with hepatic steatosis compared to those without steatosis, in particular in association with HCV genotype 3 infection.[41,42] The impact of HIV-HCV coinfection on prevalence of hepatic steatosis remains unclear.[43–45] We were unable to assess the impact of HCV genotype on lipid levels because these data were not available in our study. However, a previous analysis of HCV-infected drug users in our community found that the majority (79%) of participants were infected with either genotype 1a or 1b, with only 5% prevalence of genotype 3a.[10] Accordingly, we anticipate that the vast majority of our participants would similarly be genotype 1.

Notably, we also found markedly lower CRP in association with HCV infection. While this finding, which appears paradoxical in the presence of chronic inflammation, has not previously been reported among HIV-infected patients, it has been noted in other populations.[19,20] Nascimento et al.[20] reported lower CRP among HCV-seropositive hemodialysis patients, compared to HCV-seronegative controls also on hemodialysis. Similarly, HCV-infected patients initiating interferon alfa-2b treatment had lower baseline CRP than uninfected controls.[19] Secretion of CRP occurs primarily in the liver and it is therefore plausible that impaired hepatic function associated with chronic hepatitis may lead to decreased expression of CRP in HCV-infected patients. Interestingly, Kalabay et al.[19] found no change in CRP among those HCV-infected patients who showed a virologic response to interferon alfa-2b treatment (at least 90% decrease in HCV RNA after 3 months of therapy), suggesting that factors other than viral replication may contribute to the HCV-associated reduction in CRP.

Previous studies of HCV status in relationship to lipids and CRP have used primarily antibody testing for HCV classification.[16,31,46] The fact that detectable HCV RNA more precisely identifies individuals with active HCV replication is a major strength of this study.

The absence of HCV RNA results for anti-HCV negative men is a limitation of our study, because immunosuppressed individuals infrequently may have detectable HCV RNA despite seronegativity.[11,47] Sherman et al.,[11] using an HCV EIA 2.0 assay, reported the presence of hepatitis C viremia in 5.5% of anti-HCV–negative patients. However, we previously found no persons with detectable HCV RNA among 139 anti-HCV–negative drug users, using a third-generation EIA 3.0 assay (the assay used for the current study).[10] The availability of data on transaminase levels and markers of hepatic synthetic function would have strengthened this analysis. While we do not have such data, our study participants were ambulatory volunteers recruited from the community who were able to comply with scheduled research visits and therefore were unlikely to have debilitating end-stage liver disease. We were unable to assess the impact of recent interferon use on CRP levels in this study since the small number of men who reported recently receiving interferon (two men) precluded its use as a covariate in our multivariate analysis. Because we excluded individuals who had prior myocardial infarction or stroke from this analysis, we cannot generalize our study findings to populations with prior clinical cardiovascular events.

In summary, this study showed an association of HCV infection with markedly lower total cholesterol, LDL-C and CRP levels among older HIV-infected and at-risk men, and with lower triglycerides among HIV-infected men on HAART. Given the importance of lipids and CRP as atherosclerosis risk factors, and the need to accurately assess cardiovascular risk among HIV-infected persons, these findings have important implications for both clinicians and researchers. Our results suggest that HCV coinfection could play a protective role against development of dyslipidemia among HIV-infected persons. Although the known morbidity and mortality of liver disease from HCV coinfection remains the predominant focus of HCV evaluation among HIV-infected persons, evidence that HIV-HCV coinfected patients may be at lower risk of developing lipid abnormalities on HAART should be considered when assessing risks and benefits of different antiretroviral regimens. Lower CRP levels seen with HCV infection may also impact atherosclerosis risk, however, the predictive value of CRP as a surrogate cardiovascular risk marker has not yet been evaluated in this population. The findings of this study also highlight the need to include assessment of HCV status in studies of dyslipidemia and cardiovascular risk in the HIV-infected population. Further investigation is needed to elucidate the mechanisms underlying the lower lipid and CRP levels seen with HCV infection, and to determine relationships to liver inflammation and synthetic function.

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Table 1

Demographic and Clinical Characteristics of Participants by HCV Status

Characteristic	*HCV-uninfected* (n = *72*)	*HCV-infected* (n = *110*)	p
Age, years, median (IQR)	54 (51, 57)	54 (52, 56)	0.89
Race/ethnicity			0.06
Black	39 (54.2)	78 (70.9)	
Hispanic	21 (29.2)	18 (16.4)	
White	12 (16.7)	14 (12.7)	
HCV/HIV transmission risk factor			
Ever inject drugs	21 (29.2)	97 (88.2)	<0.001
High-risk sexual activity[a]	63 (87.5)	82 (74.6)	0.35
Blood/blood product transfusion	9 (12.5)	15 (13.6)	0.45
Waist circumference, cm, median (IQR)	90.0 (82.9, 96.6)	87.5 (81.1, 96.0)	0.26
BMI			0.11
< 25 kg/m^2	29 (40.3)	59 (53.6)	
25.0−29.9 kg/m^2	34 (47.2)	35 (31.8)	
≥ 30 kg/m^2	9 (12.5)	16 (14.5)	
Median value, kg/m^2 (IQR)	25.7 (23.1, 28.0)	24.6 (21.8, 28.7)	0.14
HOMA-IR, U/mL · mmol/L, median (IQR)	2.71 (1.70, 4.51)	3.09 (2.01, 4.96)	0.48
Diabetes mellitus	6 (8.3)	6 (5.5)	0.44
Impaired glucose tolerance	16 (22.2)	29 (26.4)	0.53
Hypertension	41 (56.9)	70 (63.6)	0.37
High-fat and low-fiber dietay intake	15 (21.1)	26 (23.9)	0.67
Current cigarette smoking	43 (59.7)	89 (80.9)	0.002
Pack-years of smoking median (IQR)	4.5 (23.0)	17.9 (7.4, 32.1)	0.35
Alcohol use in the past 6 months[b]			0.67
None	29 (42.6)	47 (44.8)	
< 1 drink/day	32 (47.1)	42 (40.0)	
2−3 drinks/day	6 (8.8)	12 (11.4)	
> 3 drinks/day	1 (1.5)	4 (3.8)	
Any drug use in past 6 months	21 (29.2)	51 (46.4)	0.02
Cocaine use in past 6 months	18 (25.0)	42 (38.2)	0.06
Heroin use in past 6 months	10 (13.9)	26 (23.6)	0.11
HIV-infected	39 (54.2)	69 (62.7)	0.25
CD4 cell count (n = 99)[c]			0.89
< 200 cells/mm^3	9 (25)	17 (27)	
200−499 cells/mm^3	20 (55.6)	32 (50.8)	
≥ 500 cells/mm^3	7 (19.4)	14 (22.2)	
Detectable HIV-1 viral load[d]	20 (52.6)	42 (62.7)	0.31
Antiretroviral category			0.16
Antiretroviral-naïve	7 (17.9)	19 (27.5)	
Non-PI HAART	12 (30.8)	11 (15.9)	
PI-based HAART	20 (51.3)	39 (56.5)	
Currently taking ritonavir	10 (25.6)	21 (30.4)	0.60

Data are no. (%) of participants, unless otherwise indicated.

HCV, hepatitis C virus; IQR, interquartile range; BMI, body mass index; HOMA-IR, homeostatis model assessment; PI, protease inhibitor; HAART, highly active antiretroviral therapy.

[a] High-risk sexual activity for men in this study defined as any of the following: sex with injection drug user or an HIV-infected partner; sex with a man; exchanging sex for drugs or money.

[b] Data on alcohol use missing for 9 participants (4 HCV-uninfected and 5 HCV-infected).

[c] Data on CD4 cell count missing for 9 of 108 HIV-infected participants.

[d] Detectable HIV-1 viral load indicates HIV-1 viral load ≥ 75 copies/mL.

Table 2

Lipid and C-Reactive Protein Levels, Stratified by HCV Status in the Overall Study Sample and in HIV-Infected Men

Parameter	*Overall study sample* (n = *182*)			*HIV-infected* (n = *108*)		
	HCV-uninfected (n = *72*)	*HCV-infected* (n = *110*)	p	*HCV-uninfected* (n = *39*)	*HCV-infected* (n = *69*)	p
Total cholesterol, mg/dL	178.4 (5.1)	143.9 (3.4)	< 0.001	176.2 (7.5)	138.4 (4.0)	< 0.001
LCL-C, mg/dL	102.0 (3.5)	78.3 (2.9)	< 0.001	99.7 (5.2)	74.3 (3.4)	< 0.001
HDL-C, mg/dL	45.5 (2.0)	44.8 (1.4)	0.81	44.0 (3.2)	41.8 (1.8)	0.80
Triglycerides, mg/dL, mg/dL	139.6 (12.0)	112.4 (7.4)	0.07	152.7 (17.1)	124.8 (10.6)	0.11
CRP, mg/L, median (IQR)[a]	1.86 (1.01, 4.92)	1.03 (0.30, 2.65)	0.04	1.78 (1.10, 4.26)	1.30 (0.30, 2.84)	0.62
CRP risk group, *n* (%)[a]			0.01			0.16
< 1 mg/dL	16 (25.0)	45 (47.9)		8 (22.9)	26 (41.9)	
1−3 mg/dL	26 (20.6)	28 (29.8)		17 (48.6)	21 (33.9)	
> 3 mg/dL	22 (34.4)	21 (22.3)		10 (28.5)	15 (24.2)	

Data are mean standard error of the mean [SEM], unless otherwise indicated.

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

[a]CRP data available for 158 men in the overall study sample (64 HCV-uninfected, 94 HCV-intected) and for 97 of the HIV-infected men (35 HCV-uninfected, 62 HCV-infected).

Table 3

Factors Associated with Lipids and CRP in the Overall Study Sample

Total cholesterol, mg/dL				*LDL-C, mg/dL*			
Parameter	***Regression coefficient***	***95% CI***	**p**	***Parameter***	***Regression coefficient***	***95% CI***	**p**
HCV-infected	−32.51	−44.52--20.50	<0.001	HCV-infected	−22.23	−31.2--13.21	<0.001
HIV-infected	−9.73	−21.68−2.23	0.11	HIV-infected	−6.57	−15.56−2.41	0.15
Age ≥ median[a]	3.61	−8.33−15.55	0.55	Age ≥ median[a]	7.66	−1.32−16.63	0.09
$\log_{10}$ (HOMA-IR)[b]	6.53	−9.82−22.87	0.43	$\log_{10}$ (HOMA-IR)[b]	13.36	1.08−25.64	0.03
High fiber, low fat dietary intake	−10.11	−24.23−4.01	0.16	High fiber, low fat dietary intake	−3.56	−14.17−7.05	0.51
$\log_{10}$ (triglycerides), mg/dL[b]				*$\log_{10}$ (CRP), mg/dL*[b]			
HCV-infected	−0.09	−0.16--0.02	0.01	HCV-infected	−0.39	−1.87--0.29	<0.001
HIV-infected	0.115	0.05−0.18	0.001	HIV-infected	0.09	−0.10−0.28	0.35
Age ≥ median[a]	−0.07	−0.14−0.001	0.05	Age ≥ median[a]	−0.12	−0.30−0.07	0.21
$\log_{10}$ (HOMA-IR)[b]	0.14	0.04−0.23	0.01	Waist circumference	0.01	0.005−0.022	0.001
High fiber, low fat dietary intake	−0.03	−0.113−0.05	0.44	Pack-years of smoking	0.006	0.002−0.01	0.003

Waist circumference measured in cm, HOMA-IR in U/mL · mmol/L.

CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

[a] Median age = 54 years.

[b] Insulin resistance as measured by homeostasis model assessment (HOMA-IR), triglycerides, and C-reactive protein were log-transformed to meet normality criteria for linear regression.

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Table 4

Factors Associated with Lipids and CRP Among HIV-Infected Men

Total cholesterol, mg/dL				*LDL-C, mg/dL*			
Parameter	***Regression coefficient***	***95% CI***	**p**	***Parameter***	***Regression coefficient***	***95% CI***	**p**
HCV-infected	−33.69	−49.20--18.18	<0.001	HCV-infected	−23.18	−35.55--10.81	<0.001
PI-HAART[a]	15.16	−3.86−34.18	0.12	PI-HAART[a]	0.12	−15.05−15.29	0.98
Non-PI-HAART[a]	−3.32	−27.18−20.54	0.78	Non-PI-HAART[a]	−2.74	−21.77−16.30	0.78
Detectable HIV-1 viral load[b]	−16.72	−32.68--0.75	0.04	Detectable HIV-1 viral load[b]	−12.07	−24.68−0.66	0.06
Age ≥ median[a]	6.04	−8.88−20.97	0.42	Age ≥ median[a]	11.10	−0.81−23.0	0.07
$\log_{10}$ (HOMA-IR)[b]	10.83	−8.92−30.59	0.28	$\log_{10}$ (HOMA-IR)[b]	15.33	−4.29−31.09	0.06
High fiber, low fat dietary intake	−17.13	−34.17−0.09	0.049	High fiber, low fat dietary intake	−6.82	−20.42−6.77	0.32
	$\log_{10}$ (triglycerides), mg/dL[a]				*$\log_{10}$ (CRP), mg/dL*[a]		
HCV-infected	0.14	−0.06−0.3	0.18	HCV-infected	−0.39	−0.65--0.13	0.004
PI-HAART[a]	0.34	0.14−0.54	0.001	PI-HAART[a]	−0.09	−0.22−0.40	0.57
Non-PI-HAART[a]	0.18	−0.05−0.41	0.13	Non-PI-HAART[a]	−0.03	−0.43−0.36	0.88
(HCV status) × (PI)	−0.29	−0.52--0.05	0.02	Detectable HIV-1 viral load[b]	0.07	−0.20−0.32	0.50
(HCV status) × (Non-PI)	−0.34	−0.62--0.06	0.02	Age ≥ median[c]	−0.05	−0.29−0.20	0.70
Detectable HIV-1 viral load[b]	0.04	−0.05−0.14	0.34	Waist circumference	0.01	−0.001−0.02	0.07
Age ≥ median[c]	−0.06	−0.15−0.03	0.17	Pack-years of smoking	0.007	0.000−0.01	0.05
$\log_{10}$ (HOMA-IR)[d]	0.12	0.000−0.24	0.049				
High fiber, low fat dietary intake	−0.05	−0.15−0.06	0.37				

Waist circumference measured in cm, HOMA-IR in U/mL · mmol/L.

CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PI, protease inhibitor; HAART, highly active antiretroviral therapy.

[a] Reference group: ARV-naïve HIV-infected men.

[b] Detectable HIV-1 viral load indicates HIV-1 viral load ≥75 copies/mL.

[c] Median age = 54 years.

[d] Insulin resistance as measured by homeostasis model assessment (HOMA-IR), triglycerides, and C-reactive protein were log-transformed to meet normality criteria for linear regression.

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